Preparation and Anticonvulsant Activity of N-Substituted Benzenedisulfonamides

GERALD F. HOLLAND, WILLIAM H. FUNDERBURK,[1] AND KENNETH F. FINGER

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut

Received December 14, 1962

A series of N-substituted-3- and -4-benzenedisulfonamides (Tables I and II) have been prepared by the reaction between 3- and 4-sulfamylbenzenesulfonyl chloride and amines, respectively. A number of other synthetic methods were not successful. The anticonvulsant and carbonic anhydrase inhibitory properties of these compounds are listed in Tables III–VII. Some show greater anticonvulsant activity than either acetazolamide or ethoxzolamide. The N-substituted-4-benzenedisulfonamides are more potent anticonvulsant agents than the N-substituted-3-benzenedisulfonamides. Within the N-substituted-4-benzenedisulfonamide series, bulky or polar substituents (R_1, R_2) decrease anticonvulsant activity. A correlation between *in vivo* inhibition of brain carbonic anhydrase and anticonvulsant activity is suggested.

Within the past few years a considerable body of literature has appeared relating to the clinical usefulness of a wide variety of benzene and heterocyclic sulfonamides. Some of these, such as the 1,2,4-benzothiadiazine-1,1-dioxides and 1,3-benzenedisulfonamides, are potent diuretic agents.[2-8] Other sulfonamides, such as acetazolamide,[9] ethoxzolamide,[10] dichlorphenamide,[11] and methazolamide,[12] which were originally developed as diuretic agents, are used now either in the treatment of glaucoma or epilepsy. The diuretic, antiglaucoma and anticonvulsant activities of these latter drugs result from their inhibiting the enzyme carbonic anhydrase[4-6,13-17] in the renal tubules, ciliary body of the eye[18,19] and brain,[20,21] respectively. The more effective 1,2,4-benzothiadiazine-1,1-dioxides have largely replaced the carbonic anhydrase inhibitors as diuretic agents.

A series of N-substituted benzenedisulfonamides was prepared during the course of a search for prototype sulfonamides. This report is a structure–anticonvulsant activity study of these compounds, inasmuch as their diuretic activity has already been shown to be qualitatively similar to that of the carbonic anhydrase inhibitors.[22]

Synthesis

N-Substituted benzenedisulfonamides were described only recently.[22,23a] Initially, the chlorosulfonation of benzenesulfonamides followed by amination was considered as a possible route to the N-substituted-3-benzenedisulfonamides. However, at elevated temperatures benzenesulfonamides react with a large excess of chlorosulfonic acid, followed by thionyl chloride, to give 3-benzenedisulfonyl chlorides. The lability of the sulfamyl group to certain acidic reagents is known.[24-26] These earlier investigators observed the formation of benzenesulfonyl chlorides when benzenesulfonamides were treated with a slight excess of either chlorosulfonic acid or phosphorus pentachloride. Our results are similar to theirs. However we observe, in addition to the cleavage of the sulfamyl group, ring chlorosulfonation when using a large excess of chlorosulfonic acid.

Further chlorosulfonation experiments were carried out employing lower temperatures and using chloroform as a solvent. These are listed below. Under these conditions cleavage of the sulfamyl group without ring chlorosulfonation takes place. It is noteworthy that at 25°, or even below 25°,[27] the conversion of a sulfamyl function to a sulfonyl chloride is

CHLOROSULFONATION EXPERIMENTS WITH 4-TOLYLSULFONAMIDE

$$p\text{-}CH_3C_6H_4SO_2NH_2 + ClSO_3H \xrightarrow[3\ hr.]{CHCl_3} p\text{-}CH_3C_6H_4SO_2Cl$$

No. of moles	No. of moles	Temp., °C.	Yield, %
1	4	61	84
1	4	25	60
1	2	25	60
1	1	25	Starting material

(1) A. H. Robins Company, Inc., Richmond, Virginia.

(2) R. M. Taylor and J. G. Topliss, *J. Med. Pharm. Chem.*, **5**, 312 (1962), and references cited in this paper.

(3) P. W. Feit, *Acta Chem. Scand.*, **16**, 297 (1962); E. Schlittler, G. de Stevens, and L. Werner, *Angew. Chem. Intern. Ed. Engl.*, **1**, 235 (1962).

(4) K. H. Beyer and J. E. Baer, "Progress in Drug Research," Vol. II, E. Jucker, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 9.

(5) H. Heller and M. Ginsburg, "Progress in Medicinal Chemistry," Vol. I, G. P. Ellis and G. B. West, Ed., Butterworths, London, 1961, p. 132.

(6) K. H. Beyer and J. E. Baer, *Pharmacol. Rev.*, **13**, 517 (1961); S. Y. P'an, A. Scriabine, D. E. McKersie, and W. M. McLamore, *J. Pharmacol. Exptl. Therap.*, **128**, 122 (1960).

(7) A. David and K. P. Fellows, *J. Pharm. and Pharmacol.*, **12**, 65 (1960).

(8) B. G. Boggiano, S. Condon, M. T. Davies, G. B. Jackman, B. G. Overell, V. Petrow, O. Stephenson, and A. M. Wild, *ibid.*, **12**, 419 (1960).

(9) Diamox ®.

(10) Cardrase ®.

(11) Daranide ®.

(12) Neptazane ®.

(13) R. O. Roblin, Jr., and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).

(14) W. H. Miller, A. M. Dessert, and R. O. Roblin, Jr., *ibid.*, **72**, 4893 (1950).

(15) R. W. Young, K. H. Wood, J. A. Eichler, J. R. Vaughan, Jr., and G. W. Anderson, *ibid.*, **78**, 4649 (1956).

(16) J. Korman, *J. Org. Chem.*, **23**, 1769 (1958).

(17) A. Lespagnol, D. Bar, E. Debrugne, and D. Sauvay, *Bull. Soc. Chim. France*, 490 (1960); J. Bourdais and F. Meyer, *ibid.*, 550 (1961).

(18) A. Posner, *Am. J. Ophthalmol.*, **45**, 225 (1958).

(19) P. J. Wistrand, J. A. Rawls, Jr., and T. H. Maren, *Acta Pharmacol. Toxicol.*, **17**, 337 (1960); W. D. Gray, T. H. Maren, G. M. Sisson, and F. H. Smith, *J. Pharmacol. Exptl. Therap.*, **121**, 160 (1957).

(20) J. G. Millichap, D. M. Woodbury, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **115**, 251 (1955).

(21) S. Solomon and A. Hirano, *Neurology*, **9**, 167 (1959).

(22) G. F. Holland, G. D. Laubach, W. M. McLamore, and A. Scriabine, Division of Medicinal Chemistry, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 13, 1960, Abstracts, p. 32N.

(23) (a) V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. and Pharmacol.*, **12**, 705 (1960); (b) A. V. Kirsanov and N. A. Kirsanova, *Zh. Obshch. Khim.*, **29**, 1802 (1959); *Chem. Abstr.*, **54**, 8693 (1960).

(24) H. Limpricht and R. Hansen, *Ber.*, **18**, 2174 (1885).

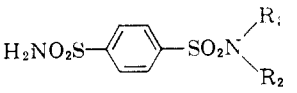
(25) W. Marckwald and A. v. Droste-Huelshoff, German Patent 105870 (Dec. 1, 1897).

(26) T. B. Johnson and E. V. McCollum, *Am. Chem. J.*, **35**, 54 (1906).

(27) J. M. Sprague, L. F. McBurney, and L. W. Kissinger, *J. Am. Chem. Soc.*, **62**, 1716 (1940).

Table I

N-Substituted-4-benzenedisulfonamides



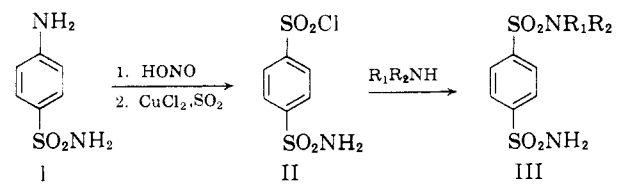
R_1	R_2	Yield, %	M.p., °C.	Formula	Analyses, % Calculated C	H	N	Found C	H	N
CH_3[a]	H	61	158–159	$C_7H_{10}N_2O_4S_2$	33.59	4.03	11.19	33.85	4.13	11.40
C_2H_5	H	64	163–164	$C_8H_{12}N_2O_4S_2$	36.37	4.58	10.60	36.13	4.45	10.69
CH_2CH_2Br	H	63	154–155	$C_8H_{11}BrN_2O_4S_2$	28.00	3.23	8.16	27.99	3.22	8.31
$CH_2CH_2CH_2Br$	H	79	161–162	$C_9H_{13}BrN_2O_4S_2$	30.26	3.67	7.84	30.47	3.70	7.92
$CH(CH_3)_2$	H	71	169–170	$C_9H_{14}N_2O_4S_2$	38.83	5.07	10.07	38.73	4.99	10.13
$CH_2CH{=}CH_2$	H	69	154–155	$C_9H_{12}N_2O_4S_2$	39.11	4.38	10.14	39.01	4.45	9.89
$CH_2CH_2CH_3$	H	76	171–173	$C_9H_{14}N_2O_4S_2$	38.83	5.07	10.07	38.83	5.31	9.89
$CH_2C(CH_3){=}CH_2$	H	80	184–185	$C_{10}H_{14}N_2O_4S_2$	41.38	4.86	9.65	41.41	4.91	9.78
$CH_2CH_2CH_2OCH_3$	H	71	159–160	$C_{10}H_{16}N_2O_5S_2$	38.96	5.23	9.09	38.76	5.06	9.12
n-C_4H_9	H	84	171–172	$C_{10}H_{16}N_2O_4S_2$	41.10	5.52	9.59	41.00	5.44	9.58
n-C_7H_{15}	H	81	179–180	$C_{13}H_{22}N_2O_4S_2$	46.70	6.63	8.39	46.62	6.66	8.42
CH_2COOH	H	81	234–235	$C_8H_{10}N_2O_6S_2$	32.65	3.42	9.52	32.61	3.55	9.63
$(CH_2)_2COOH$	H	28	195–196	$C_9H_{12}N_2O_6S_2$	35.06	3.92	9.09	34.75	3.87	9.05
$(CH_2)_3COOH$	H	74	176–177	$C_{10}H_{14}N_2O_6S_2$	37.26	4.38	8.69	37.20	4.56	8.28
CH_2CONH_2	H	71	242–243	$C_8H_{11}N_3O_5S_2$	32.76	3.78	14.33	32.51	3.90	14.54
$CH_2CONHC_3H_7$	H	95	145–146	$C_{11}H_{17}N_3O_5S_2$	39.39	5.11	12.53	39.20	5.37	12.51
$CH_2CONHNH_2$	H	69	191–192	$C_8H_{12}N_4O_5S_2$	31.16	3.92	18.17	30.72	4.10	18.29
$CH_2COOC_2H_5$	H	52	184–185	$C_{10}H_{14}N_2O_6S_2$	37.26	4.38	8.69	37.12	4.45	8.65
C_6H_{11}	H	60	202–203	$C_{12}H_{18}N_2O_4S_2$	45.26	5.70	8.80	44.92	5.66	9.20
$-(CH_2)_5-$		48	220–221	$C_{11}H_{16}N_2O_4S_2$	43.40	5.30	9.21	43.43	5.26	9.16
$-(CH_2)_2O(CH_2)_2-$		68	192–193	$C_{10}H_{14}N_2O_5S_2$	39.22	4.61	9.15	39.47	4.67	9.09
C_6H_5	H	79	230–231	$C_{12}H_{12}N_2O_4S_2$	46.16	3.87	8.97	46.24	3.99	9.08
4-$(CH_3)_2NC_6H_4$	H	80	243 dec.	$C_{14}H_{17}N_3O_4S_2$	47.32	4.82	11.83	47.35	4.99	11.95
3-$CF_3C_6H_4$	H	52	167–168	$C_{13}H_{11}F_3N_2O_4S_2$	41.05	2.92	7.37	40.71	2.77	7.66
4-ClC_6H_4	H	95	252–253	$C_{12}H_{11}ClN_2O_4S_2$	41.55	3.20	8.08	41.06	3.22	7.67
$C_6H_5CH_2$	H	60	196–197	$C_{14}H_{14}N_2O_4S_2$	47.84	4.32	8.58	47.90	4.14	8.49
2-$ClC_6H_4CH_2$	H	91	173–174	$C_{13}H_{13}ClN_2O_4S_2$	45.27	3.63	7.77	45.11	4.43	7.67
4-$ClC_6H_4CH_2$	H	79	204–205	$C_{13}H_{13}ClN_2O_4S_2$	45.27	3.63	7.77	43.48	4.14	7.80
$C_6H_5CH_2CH_2$	H	97	190–191	$C_{14}H_{16}N_2O_4S_2$	49.41	4.74	8.23	49.86	4.90	8.45
(+)-$C_6H_5CH_2CH(CH_3)$-[b]	H	77	172–173	$C_{15}H_{18}N_2O_4S_2$	50.85	5.12	7.91	50.57	5.00	7.92
1-$C_{10}H_7$	H	33	241–242	$C_{16}H_{14}N_2O_4S_2$	53.02	3.89	7.73	52.98	4.03	7.95
C_2H_5	C_2H_5	62	158–160	$C_{10}H_{16}N_2O_4S_2$	41.10	5.52	9.59	41.30	5.37	9.68
2-$ClC_6H_4CH_2$	CH_3	83	184–185	$C_{14}H_{15}ClN_2O_4S_2$	44.86	4.03	7.48	44.94	4.12	7.42
4-$ClC_6H_4CH_2$	CH_3	66	182–183	$C_{14}H_{15}ClN_2O_4S_2$	44.86	4.03	7.48	44.50	4.13	7.56
$C_6H_5CH_2$	$C_6H_5CH_2$	27	178–179	$C_{26}H_{26}N_2O_4S_2$	57.67	4.84	6.73	57.54	4.89	6.80

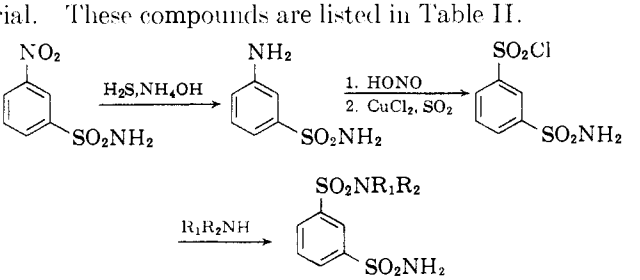
[a] Reference 23a, m.p. 160–161°. [b] $[\alpha]^{23.5}D$ +58.9° (*c* 1.03, *N* NaOH).

quite facile. Also, only starting material is recovered when equimolar amounts of 4-tolylsulfonamide and chlorosulfonic acid are reacted together.

Inasmuch as the chlorosulfonation method to N-substituted benzenedisulfonamides was not feasible, attention was turned to other synthetic routes. Recently, Meerwein, *et al.*,[28] reported on the preparation of benzenesulfonyl chlorides by diazotization of anilines, followed by treatment of the diazonium complex with an acetic acid solution containing sulfur dioxide and cupric chloride. No mention was made of the applicability of this nitrosation reaction, which is carried out in strong acid, to anilines containing a sulfamyl moiety.[23a,b] A 42% yield of 4-sulfamylbenzenesulfonyl chloride (II) is obtained from sulfanilamide under these conditions. Reaction between II and various amines leads to the desired N-substituted-4-benzenedisulfonamides (III). These compounds are described in Table I.

The N-substituted-3-benzenedisulfonamides are prepared by essentially the same procedure, except that 3-nitrobenzenesulfonamide serves as the starting material. These compounds are listed in Table II.





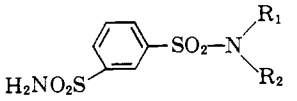
Results and Discussion

The N-substituted benzenedisulfonamides were screened in male mice for anticonvulsant activity by

(28) H. Meerwein, G. Dittmar, R. Gollner, K. Hafner, F. Mensch, and D. Steinfort, *Chem. Ber.*, **90**, 841 (1957).

TABLE II

N-SUBSTITUTED-3-BENZENEDISULFONAMIDES

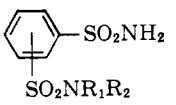


R_1	R_2	Yield, %	M.p., °C.	Formula	Analyses, % Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
$CH(CH_3)_2$	H	68	145–146	$C_9H_{14}N_2O_4S_2$	38.83	5.07	10.07	39.09	5.16	10.05
CH_2CH_2Br	H	86	159–160	$C_8H_{11}BrN_2O_4S_2$	28.00	3.23	8.16	28.26	3.28	8.28
3-$CF_3C_6H_4$	H	69	127–128	$C_{13}H_{11}F_3N_2O_4S_2$	41.05	2.92	7.37	41.68	3.09	7.16
$C_6H_5CH_2$	H	87	132–133	$C_{13}H_{14}N_2O_4S_2$	47.84	4.32	8.58	47.34	4.89	8.40
(+)-$C_6H_5CH_2CH(CH_3)$[a]	H	64	140–141	$C_{15}H_{18}N_2O_4S_2$	50.85	5.12	7.91	51.15	5.16	8.04

[a] $[\alpha]^{25.4}D$ +48.7° (*c* 1.03, *N* NaOH).

TABLE III

ANTICONVULSANT ACTIVITY (MOUSE, I. P., ELECTROSHOCK) OF N-SUBSTITUTED BENZENEDISULFONAMIDES



PD_{50}, <30 mg./kg. R_1	R_2	PD_{50}, 30–135 mg./kg. R_1	R_2	PD_{50}, 135–250 mg./kg. R_1	R_2	PD_{50}, 250–500 mg./kg. R_1	R_2	PD_{50}, >500 mg./kg. R_1	R_2
4[a] H	C_2H_5	acetazolamide		4 H	H	4 H	CH_2COOH	4 H	C_7H_{15}
4 H	$CH(CH_3)_2$	ethoxzolamide		4 H	$(CH_2)_2COOH$	4 H	$CH_2CONHC_6H_7$	4 H	$C_6H_4N(CH_3)_2$-4
4 H	$(CH_2)_3OCH_3$	4 H	CH_3	4 H	$(CH_2)_3COOH$	4 H	$CH_2COOC_2H_5$	4 H	$C_{10}H_7$-1
4 H	$CH_2C_6H_5$	4 H	$(CH_2)_2Br$	4 H	CH_2CONH_2	4 H	$C_6H_4CF_3$-3	3 H	$(CH_2)_2Br$
4	$(C_2H_5)_2$	4 H	$(CH_2)_3Br$	4 H	$CH_2CONHNH_2$	4	$(CH_2C_6H_5)_2$	3 H	$C_6H_4CF_3$-3
4	—$(CH_2)_5$—	4 H	C_3H_7	4 H	$CH_2C_6H_4Cl$-4	4 H	$(CH_2)_2C_6H_5$	3 H	$CH(CH_3)CH_2C_6H_5$-(+)
4	—$(CH_2)_2O(CH_2)_2$—	4 H	C_4H_9	4 H	$CH(CH_3)CH_2C_6H_5$-(+)	3 H	H		
		4 H	C_5H_{11}	3 H	$CH_2C_6H_5$				
		4 H	$CH_2CH{=}CH_2$						
		4 H	$CH_2CH(CH_3){=}CH_2$						
		4 H	C_6H_5						
		4 H	C_6H_4Cl-4						
		4 H	$CH_2C_6H_4Cl$-2						
		4 CH_3	$CH_2C_6H_4Cl$-2						
		4 CH_3	$CH_2C_6H_4Cl$-4						
		3 H	$CH(CH_3)_2$						

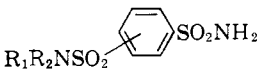
[a] The arabic numeral preceding the functional groups R_1, R_2 represents the position of the second sulfamyl moiety on the benzeuesulfonamide.

measuring protection against electroshock convulsions after intraperitoneal administration. The anticonvulsant activities of the compounds described in Tables I and II are listed in Table III. A number of N-substituted-4-benzenedisulfonamides have a PD_{50} (dose necessary to prevent hind-leg extension in 50% of animals) of less than 30 mg./kg. and are more active than either acetazolamide or ethoxzolamide. In this series, substituents (R_1,R_2) which are lipophilic in nature, such as alkyl, haloalkyl, aryl and aralkyl, generally have a favorable effect on anticonvulsant activity. However, increasing the size of the lipophilic substituent, for example, heptyl, phenethyl, etc., decreases activity. Replacing the substituents R_1,R_2 with more polar functions, such as acid, amide or ester, also reduces anticonvulsant activity. In Table IV a comparison of the anticonvulsant activity of some 1,3 and 1,4-benzenedisulfonamides is made. In all cases the 1,4-benzenedisulfonamides are more active.

Further pharmacological studies were carried out because of the potent anticonvulsant activity of some of these compounds. A number of the benzenedisulfonamides were screened *in vitro*, as inhibitors of the enzyme carbonic anhydrase. In Table V a comparison is made between the anticonvulsant activity and the increasing *in vitro* carbonic anhydrase inhibitory activity of some of these compounds. Although only a

TABLE IV

COMPARISON OF ANTICONVULSANT ACTIVITY (MOUSE, I. P., ELECTROSHOCK) OF 1,4 AND 1,3-BENZENEDISULFONAMIDES



R_1	R_2	PD_{50} range, mg./kg. 1,4-isomer	PD_{50} range, mg./kg. 1,3-isomer
H	H	135–250	250–500
H	$CH(CH_3)_2$	<30	30–135
H	$(CH_2)_2Br$	30–135	>500
H	$CH_2C_6H_5$	<30	135–250
H	$C_6H_4CF_3$-3	250–500	>500
H	$CH(CH_3)CH_2C_6H_5$-(+)	135–250	>500

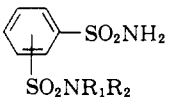
limited number were selected, the N-substituted-3-benzenedisulfonamides were less effective *in vitro* inhibitors than the N-substituted-4-benzenedisulfonamides. Also, a number of the N-substituted-4-benzenedisulfonamides are of the same order of *in vitro* activity as acetazolamide. The potent *in vitro* carbonic anhydrase inhibitory activity of the thiazide, benzthiazide,[29] has already been commented on.[6] Direct correlation between *in vitro* carbonic anhydrase inhibition and anticonvulsant activity is, of course, not possible. High activity in the former, although of first

(29) NaClex ®.

order of importance for intrinsic *in vivo* carbonic anhydrase inhibitory activity, does not ensure that an adequate concentration of drug will be in the brain. More meaningful would be the correlation between the *in vivo* inhibition of brain carbonic anhydrase and the anticonvulsant activity of these compounds.[29]

TABLE V

COMPARISON OF ANTICONVULSANT ACTIVITY (ELECTROSHOCK) AND *In Vitro* CARBONIC ANHYDRASE INHIBITORY ACTIVITY OF N-SUBSTITUTED BENZENEDISULFONAMIDES



	R_1	R_2	*In vitro* molar concentration producing 50% inhibition	PD_{50} range (mg./kg.) anticonvulsant activity (mouse, i.p., electroshock)
3	H	$CH_2C_6H_5$	2×10^{-6}	135–250
3	H	$CH(CH_3)_2$	9×10^{-7}	30–135
	Chlorothiazide		5×10^{-7}	
4	H	$CH(CH_3)_2$	4.2×10^{-7}	21 ± 3
4		$-(CH_2)_5-$	5×10^{-8}	<30
4	H	$(CH_2)_2Br$	3×10^{-8}	30–135
4	H	$CH_2CONHNH_2$	3×10^{-8}	135–250
4	$(CH_2C_6H_5)_2$		2.5×10^{-8}	250–500
4	H	C_6H_{11}	2.5×10^{-8}	30–135
4	H	CH_2CONH_2	2×10^{-8}	135–250
4	H	$CH_2C_6H_5$	2×10^{-8}	31 ± 4
	Acetazolamide		2×10^{-8}	134 ± 19
	Benzthiazide		2×10^{-8}	

Toward this end, three compounds, N-isopropyl-4-benzenedisulfonamide, acetazolamide, and benzthiazide were tested as *in vivo* inhibitors of brain carbonic anhydrase. They were administered (s.c.) to male mice in doses ranging from 2.5–200 mg./kg. After 1 hr. the animals were sacrificed and the carbonic anhydrase activity determined after rapid removal and homogenization of the brains in normal saline. The results (Table VI) indicate that while N-isopropyl-4-benzenedisulfonamide (50% inhibition at 4.2×10^{-7} *M*) was less potent than acetazolamide (50% inhibition at 2×10^{-8} *M*) *in vitro*, it is equal to or slightly greater than acetazolamide as an *in vivo* carbonic anhydrase inhibitor. Benzthiazide, although potent *in vitro* (50% inhibition at 2×10^{-8} *M*), has little effect on *in vivo* brain carbonic anhydrase. The difference between the *in vitro* and *in vivo* inhibitory activities of N-isopropyl-4-benzenedisulfonamide may be attributed to its different distribution ratio between the blood and brain tissue. The potent anticonvulsant and *in vivo* carbonic anhydrase inhibitory activity of N-isopropyl-4-benzenedisulfonamide suggests, for the N-substituted benzenedisulfonamides, correlation between *in vivo* carbonic anhydrase inhibition and anticonvulsant activity. It is noteworthy that although benzthiazide is a potent *in vitro* inhibitor of carbonic anhydrase it has negligible *in vivo* activity and it is not an anticonvulsant agent.[6] Physical parameters, including lipid and aqueous solubility, size, steric hinderance, acidity, etc., must play an important part in determining absorption, distribution and intrinsic carbonic anhydrase inhibitory activity of these N-substituted benzenedisulfonamides in the brain.

TABLE VI

EFFECT OF VARIOUS CARBONIC ANHYDRASE INHIBITORS ON THE ENZYMATIC ACTIVITY OF THE MOUSE BRAIN

Inhibitor	Dose mg./kg. (s.c.)	Relative enzymatic activity[a] — Dilution[b] 1/10	1/25	1/50	1/100	1/200
N-Isopropyl-4-benzenedisulfonamide	100	0.18	0.27	0.37	0.49	0.59
Acetazolamide	100	.15	.24	.26	.49	.66
Benzthiazide	100	1.00	.73	.74	.93	1.45

[a] Ratio of enzyme activity of the treated to the non-treated animals. [b] Brain tissue was homogenized and diluted to the indicated value with normal saline.

The anticonvulsant activity of N-isopropyl-4-benzenedisulfonamide was investigated further. The compound protects mice not only from convulsions produced by electroshock but also those from pentylenetetrazol.[30] However, it has no effect against strychnine in oral doses up to 300 mg./kg. or intraperitoneal doses up to 177 mg./kg. The PD_{50} (mouse, i.p.) for antagonism of electroshock seizures for N-isopropyl-4-benzenedisulfonamide, acetazolamide and ethoxzolamide is 21 ± 3 mg./kg., 134 ± 19 mg./kg. and 65 ± 16 mg./kg., respectively. It is less potent than diphenylhydantoin[31] against electroshock seizures but slightly more potent than phenobarbital. The PD_{50} (mouse, i.p.) for antagonism of pentylenetetrazol seizures for N-isopropyl-4-benzenedisulfonamide and trimethadione[32] is 171 ± 17 mg./kg. and 218 ± 25 mg./kg., respectively. N-Isopropyl-4-benzenedisulfonamide is well absorbed orally and only slightly more of it is required when given by this route. The anticonvulsant activities of this compound and standards are listed in Table VII.

Experimental

Chemical.[33] **4-Sulfamylbenzenesulfonyl Chloride.**[23a,b]—Into a 3-neck flask was placed 64 g. (0.372 mole) of sulfanilamide, 125 ml. of water and 63 ml. (0.74 mole) of concentrated hydrochloric acid. A saturated aqueous solution of sodium nitrite (26.5 g., 0.37 mole) was added at such a rate that the temperature did not rise above 0°. This solution was added with cooling and vigorous stirring to 350 ml. of a freshly prepared saturated solution of sulfur dioxide in glacial acetic acid, which contained 15 g. of cupric chloride dihydrate. After 10 min. the vigorous evolution of nitrogen subsided and the mixture was diluted with ice water. The product was collected by suction filtration and washed well with cold water. There was obtained 40 g. (42% yield). It was recrystallized from chloroform, m.p. 155–156°.

Anal. Calcd. for $C_6H_6ClNO_4S_2$: C, 28.18; H, 2.37; N, 5.48. Found: C, 27.90; H, 2.38; N, 5.20.

3-Sulfamylbenzenesulfonyl Chloride.[23a]—By using essentially the same procedure as above, a 60% yield of 3-sulfamylbenzenesulfonyl choride was formed from 3-aminobenzenesulfonamide,[34] m.p. 155–156°.

Anal. Calcd. for $C_6H_6ClNO_4S_2$: C, 28.18; H, 2.37; N, 5.48. Found: C, 28.11; H, 2.38; N, 5.51.

Preparation of N-Substituted Benzenedisulfonamides. N-3-Methoxypropyl-4-sulfamylbenzenesulfonamide.—A solution of 10 g. (0.039 mole) of 4-sulfamylbenzenesulfonyl chloride and 11 g. (0.12 mole) of 3-methoxypropylamine in 150 ml. of chloroform was refluxed for 16 hr. The chloroform was removed *in vacuo* and the residue washed well with *N* hydrochloric acid and water. After filtering, there was obtained 8.5 g. (71% yield) of product, m.p. 158–160°. It was recrystallized from aqueous ethanol, m.p.

(30) Metrazol ®.
(31) Dilantin ®.
(32) Tridione ®.
(33) All melting points are corrected.
(34) F. Dobson and R. T. Williams, *Biochem. J.*, **40**, 215 (1946).

TABLE VII

ANTICONVULSANT ACTIVITY (MOUSE, PD_{50} MG./KG.)

Compound	Route of administration	Pentylenetetrazol[a]	Electroshock	Strychnine[b]
N-Isopropyl-4-benzenedisulfonamide	i.p.	171 ± 17	21 ± 3	None up to 177
N-Isopropyl-4-benzenedisulfonamide	p.o.	207 ± 33	34 ± 4	None up to 300
Acetazolamide	i.p.	Weak	134 ± 19	
Ethoxzolamide	i.p.	354 ± 46	65 ± 16	
Trimethadione	i.p.	218 ± 25		
Diphenylhydantoin	i.p.		6.6 ± 0.6	
Phenobarbital	i.p.		24 ± 3	
N-Benzyl-4-benzenedisulfonamide	i.p.	>266	31 ± 4	

[a] Reference 35. [b] G. Chen, C. R. Ensor, and R. Portman, *Arch. Intern. Pharmacodyn.*, **104**, 333 (1956).

159–160°. The compounds in Table I and II, with the exception of those listed below, were prepared by this method.

N-2-Bromoethyl-3-sulfamylbenzenesulfonamide.—A mixture of 10 g. (0.039 mole) of 3-sulfamylbenzenesulfonyl chloride, 7.8 g. (0.039 mole) of 2-bromoethylamine hydrochloride and 11 ml. (0.08 mole) of triethylamine in 100 ml. of methylene chloride was stirred overnight at 25°. The methylene chloride was removed *in vacuo* and the residue washed well with water, *N* hydrochloric acid and water. After filtering, there was obtained 11.8 g. (86% yield) of product which was recrystallized from aqueous acetone, m.p. 159–160°.

N-2-Bromoethyl-4-sulfamylbenzenesulfonamide and N-3-bromopropyl-4-sulfamylbenzenesulfonamide were prepared by the same procedure.

4-(4-Sulfamylbenzenesulfonamido)butyric Acid.—A mixture of 13 g. (0.05 mole) of 4-sulfamylbenzenesulfonyl chloride and 5 g. (0.05 mole) of 4-aminobutyric acid in 100 ml. of *N* sodium hydroxide was stirred at 25° for 16 hr. A white precipitate formed on acidification with *N* hydrochloric acid. It was removed by suction filtration and washed with cold water, 11.8 g. (74% yield), m.p. 174–175°. The product was recrystallized from water, m.p. 176–177°.

3-(4-Sulfamylbenzenesulfonamido)propionic acid and 4-sulfamylbenzenesulfonamidoacetic acid were prepared by the same method.

Ethyl 2-(4-Sulfamylbenzenesulfonamido) Acetate.—To a cooled chloroform solution of 10 g. (0.039 mole) of 4-sulfamylbenzenesulfonyl chloride and 5.5 g. (0.039 mole) of glycine ethyl ester hydrochloride was added dropwise 11 ml. (0.08 mole) of triethylamine. After 20 hr. at 25°, the chloroform was removed *in vacuo* and the product collected and washed well with water. On recrystallization from aqueous ethanol, there was obtained 6.5 g. (52% yield), m.p. 184–185°.

2-(4-Sulfamylbenzenesulfonamido)acetamide.—A mixture of 12.6 g. (0.04 mole) of ethyl 2-(4-sulfamylbenzenesulfonamido) acetate and excess ammonium hydroxide was stirred at 25° for 12 hr. The excess ammonia was driven off *in vacuo*, and the white precipitate was filtered and washed with cold water, 8.1 g. (71% yield), m.p. 242–243°. It was recrystallized from water, m.p. 242–243°.

N-Propyl-2-(4-sulfamylbenzenesulfonamido)acetamide.—A solution of 10 g. (0.031 mole) of ethyl 2-(4-sulfamylbenzenesulfonamido) acetate and 11.1 g. (0.186 mole) of propylamine in 200 ml. of methyl alcohol was heated to reflux for 16 hr. The mixture was concentrated *in vacuo* and the residue washed with cold water. On filtering there was obtained 10 g. (95% yield), m.p. 143–145°. The product was recrystallized from aqueous ethanol, m.p. 145–146°.

2-(4-Sulfamylbenzenesulfonamido)acetic Acid Hydrazide.—A mixture of 10 g. (0.031 mole) of ethyl 2-(4-sulfamylbenzenesulfonamido) acetate and 14.4 ml. (0.3 mole) of hydrazine hydrate in 250 ml. of absolute ethanol was heated to reflux for 2 hr. The solvent was removed *in vacuo* and the residue recrystallized from water, 6.5 g. (69% yield), m.p. 191–192°.

3-Benzenedisulfonyl Chloride from the Reaction of Benzenesulfonamide and Chlorosulfonic Acid at 125°.—Chlorosulfonic acid (46.6 g., 0.4 mole) was added dropwise with cooling to 15.7 g. (0.1 mole) of benzenesulfonamide over a period of 30 min. When the addition was complete the mixture was heated to 125° for 3 hr., cooled and 14.7 ml. (0.2 mole) of thionyl chloride added. The temperature was then maintained at 80° for another 90 min. After cooling, the mixture was cautiously poured into 400 ml. of cracked ice. 3-Benzenedisulfonyl chloride was collected by suction filtration and dried *in vacuo*, 20 g. (75% yield), m.p. 56–58°. The product had an identical infrared spectrum and a purified sample did not depress a mixture melting point with authentic 3-benzenedisulfonyl chloride. A portion of this material was treated with ammonium hydroxide; melting point, mixture melting point with authentic 3-benzenedisulfonamide and comparison of infrared spectra showed this product to be identical with 3-benzenedisulfonamide.

Under the same conditions 4-tolylsulfonamide gave 4-methyl-3-benzenedisulfonyl chloride.

4-Tolylsulfonyl Chloride from the Reaction of 4-Tolylsulfonamide and Chlorosulfonic Acid in Chloroform.—To a solution of 4.25 g. (0.025 mole) of 4-tolylsulfonamide in 10 ml. of chloroform was added at 25° 6.5 ml. (0.1 mole) of chlorosulfonic acid. After heating to reflux for 1 hr., the mixture was cooled and diluted with 30 ml. of ethyl acetate and 20 ml. of water. The organic layer was collected, dried and concentrated *in vacuo*. There was obtained 4.0 g. (84% yield) of 4-tolylsulfonyl chloride, m.p. 63–65°. The product had an identical spectrum and a purified sample did not depress a mixture melting point with authentic 4-tolylsulfonyl chloride. Small portions were treated with ammonium hydroxide and benzylamine; melting point, mixture melting point with authentic 4-tolylsulfonamide and N-benzyl-4-tolylsulfonamide, respectively, and comparison of infrared spectra showed the products to be 4-tolylsulfonamide and N-benzyl-4-tolylsulfonamide, respectively.

The reactions of 4-tolylsulfonamide and chlorosulfonic acid in chloroform at 25° were carried out in the same manner.

Pharmacology. Anticonvulsant Methodology.—The compounds to be tested were finely ground in a mortar with 1 drop of Tween 80 and then suspended in the appropriate amount of deionized water. They were administered to Swiss-Webster male mice weighing 17–25 g. by intraperitoneal injection in volumes of approximately 0.25 ml. Only protection from maximal electroshock seizures, indicated by hind-leg extension, was considered in testing for anticonvulsant activity.[35] The stimulus was alternating current of 50 ma. intensity with a duration of 0.2 sec. applied through corneal electrodes from a Hans Technical Associates Stimulator. This amount of current is approximately 6 times threshold. The electroshock challenge was given in all cases 1 hr. following the administration of the compound. No animal was shocked more than once. The latency of each seizure was recorded to evaluate the results better. The latency was measured from the beginning of the current to the beginning of hind-leg extension.

The dose of compound necessary to prevent hind-leg extension in 50% of the animals (PD_{50}) and standard deviations were calculated by the method of moving averages employing quantal data.[36] The animals were given a minimum of 4 geometrically spaced doses of the test drug utilizing 5 mice per dose. Since, for this method, it is necessary to select the 4 doses ranging from very low activity to very high activity many more than the minimum of 20 animals were frequently used for each compound. It should be noted that some compounds gave inconsistent results if they were not finely ground before suspending in aqueous solution.

Carbonic Anhydrase Inhibition Methodology.—*In vitro* carbonic anhydrase activity was determined by a modification of the colorimetric method of Philpot and Philpot.[37] The activity was

(35) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(36) W. R. Thompson and C. S. Weil, *Biometrics*, **8**, 51 (1952).

(37) F. J. Philpot and J. Philpot, *Biochem. J.*, **30**, 2191 (1936).

expressed in terms of enzyme units and calculated from the expression

$$\text{E.U.} = \frac{T_0 - T}{T}$$

where E.U. represents enzyme units, T_0 the time of the uncatalyzed reaction in sec., and T the time of the catalyzed reaction in sec. All reactions were carried out in a cold room maintained at 5 ± 1°. The inhibitors were preincubated with the enzyme for 10 min. prior to the addition of substrate. This procedure allowed for enzyme-inhibitor equilibrium to take place. The concentration required to inhibit 50% of the enzyme activity was determined graphically. Approximately two units of enzyme activity were utilized in each experiment.

The *in vivo* inhibition of brain carbonic anhydrase was approximated by diluting the tissue throughout a range of 1–10 to 1–200 and determining the enzyme activity of the inhibited tissue relative to the untreated controls.

Acknowledgment.—The authors wish to acknowledge the assistance of Messrs. Robert Sacco, Douglas Albot, and Norman Glidden in the preparation and Messrs. Robert Cavanaugh, Robert McNeil, and David Zaharic in the pharmacological evaluation of these compounds.

The Synthesis of Some Substituted *m*-Benzenedisulfonamides

JOHN G. TOPLISS, MARIA C. DALY, ANET LIPSKI, ELIZABETH P. SHAPIRO, AND NATHAN SPERBER

Medicinal Chemical Research Department, Schering Corporation, Bloomfield, New Jersey

Revised manuscript received December 4, 1962

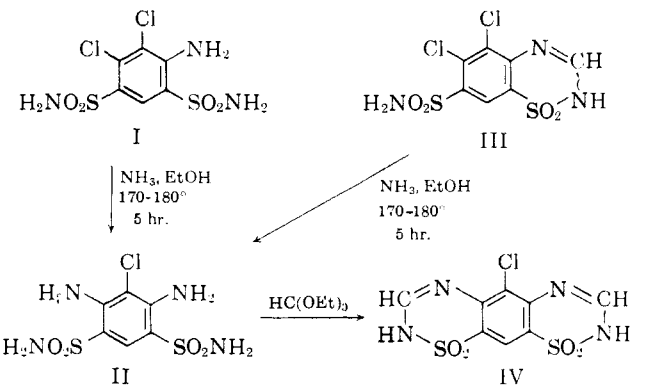
An approach to the synthesis of some substituted *m*-benzenedisulfonamides, not readily available *via* the usual methods for preparing this class of compounds, is described. The diuretic activity of the compounds was evaluated.

Prior to 1957 there was little mention of substituted *m*-benzenedisulfonamides in the organic chemical literature. Lustig and Katscher,[1] in 1927, described a convenient method for the preparation of amino substituted *m*-benzenedisulfonamides by the direct chlorosulfonation of a substituted aniline in the presence of sodium chloride, then treatment of the resulting *m*-disulfonyl chloride with ammonia. Davies and Poole[2] prepared 4,6-dichloro-*m*-benzenedisulfonamide and 2,4,6-trichloro-*m*-benzenedisulfonamide by disulfonation of the corresponding chlorobenzene and transformation of a salt of the disulfonic acid to the disulfonyl chloride with phosphorus pentachloride and thence into the disulfonamide.

With the discovery[3] that substituted *m*-benzenedisulfonamides had pronounced diuretic activity, the literature on such compounds has greatly expanded. The procedure of Lustig and Katscher has been extensively applied to substituted anilines.[3-9] The chlorosulfonation of a substituted 2-aminobenzenesulfonamide is a varient which has been used to advantage.[10] A reaction developed by Meerwein[11] for converting an amino group into a sulfonyl chloride was employed by Petrow[12] in the synthesis of benzenedisulfonamides.

We were interested in synthesizing *m*-benzenedisulfonamides for their evaluation as diuretic agents and also as intermediates for the synthesis of substituted 3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxides.[13] During the course of this work it became apparent that the methods reviewed in the preceding paragraph were not adequate for the convenient synthesis of certain *m*-benzenedisulfonamides and it is the purpose of this paper to discuss an additional approach which we have found to be very useful in the synthesis of these compounds.

The approach in question is dependent upon the activating effect of sulfamoyl groups *ortho* and *para* to a suitable leaving group (halogen or nitro) in the benzene nucleus.[14] Thus reaction of 4-amino-5,6-dichloro-*m*-benzenedisulfonamide (I) with ammonia in ethanol at 170-180° for 5 hr. furnished 5-chloro-4,6-diamino-*m*-benzenedisulfonamide (II) in satisfactory yield. This compound (II) also was obtained under similar reaction conditions from 5,6-dichloro-2H-1,2,4-



(1) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).
(2) W. Davies and H. G. Poole, *J. Chem. Soc.*, 1122 (1927).
(3) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).
(4) F. C. Novello, U. S. Patent 2,809,194, Oct. 8, 1957.
(5) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).
(6) J. H. Short and U. Biermacher, *ibid.*, **82**, 1135 (1960).
(7) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. de Stevens, *ibid.*, **82**, 1161 (1960).
(8) H. L. Yale, K. Losee, and J. Bernstein, *ibid.*, **82**, 2042 (1960).
(9) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960).
(10) C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959).
(11) (a) H. Meerwein, E. Büchner, and K. Van Emster, *J. prakt. Chem.*, [2] **152**, 237 (1939); (b) H. Meerwein, G. Dittmar, G. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).
(12) V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. and Pharmacol.*, **12**, 705 (1960).
(13) J. G. Topliss, M. H. Sherlock, F. H. Clarke, M. C. Daly, B. Pettersen, J. Lipski, and N. Sperber, *J. Org. Chem.*, **26**, 3842 (1961).
(14) Subsequent to the completion of our work the use of this principle was reported by (a) G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. and Pharmacol.*, **12**, 648 (1960), and (b) C. W. Whitehead and J. J. Traverso, *J. Org. Chem.*, **27**, 951 (1962). The particular reactions involved, however, were not the same.